to life, but much more important, life to years. Establishing this single fact has required the work of some of our best scientific minds, great cost, and enormous effort. We, as clinicians, must see to the application of this information for the benefit of our patients.

REFERENCES

1. Crowley, L. G.: Current status of the management of patients with endocrine-sensitive tumors. Part I: Introduction and carcinoma of the breast, Calif. Med., 110:43-60, Jan. 1969. Crowley, L. G., and Duwe, S. A.: Current status of the management of patients with endocrine-sensitive tumors. Part II: Carcinoma of the prostate, endometrium, thyroid, kidney and miscellaneous tumors, Calif. Med., 110: 139-150, Feb. 1969.

2. Pincus, G., and Vollmer, E., editors, Biological Activities of Steroids in Relation to Cancer, Academic Press, New York, 1960, p. 381.

Guest Editorial

Erythroblastosis Fetalis—Now a Preventable Disease

A WELL-KNOWN PROVERB states that "an ounce of prevention is worth a pound of cure." Modern medicine multiplies this differential not merely 16 times but usually many hundred- or thousand-fold. With continued medical progress, more and more conditions are responding to the preventive use of micrograms of material administered in a few minutes when, formerly, days of effort and kilograms of drugs—not to mention untold hours of anxiety—were expended in treatment of serious disease. A recent example of this kind of progress is the prevention of erythroblastosis fetalis, more properly described by the term "hemolytic disease of the fetus and newborn" due to maternal Rh antibody.

This past year, there became available commercially* a gamma globulin concentrate of anti-Rh serum. This material, called RhoGAM®, will block or prevent the immunization or sensitization of an Rh-negative woman recently delivered of an Rh-positive infant. Previously, each such pregnancy represented a risk of 1 percent to 10 percent, or more, of inducing Rh antibody production. This, in a subsequent Rh-positive pregnancy, could produce hemolytic disease of the fetus and newborn in varying degree — from the severest form (ending in death of the infant *in utero*) to the less acute type (showing anemia at birth) and mild varieties (having compensated anemia and jaundice, but treatable after birth). With four million pregnancies in the United States in 1960, it is estimated that erythroblastosis fetalis accounted for about 10,000 stillbirths and 40,000 live-born affected infants. Of this latter group, some 36,000 to 38,000 recovered, usually only after prompt and sometimes repeated exchange transfusions. This is the dimension of the problem that the gamma globulin treatment can eliminate.

In order to appreciate the importance of this new advance in preventive medicine, it may be helpful to review briefly the steps in the recognition and treatment of erythroblastosis fetalis due to Rh-incompatibility between mother and infant. Although the condition was described in its various forms during the previous 40 years, it was not considered an entity until 1932. The etiology remained obscure until 1939, when Levine, after studying a case of intragroup hemolytic transfusion reaction (a group O woman receiving a pint of her husband's group O blood), concluded that the patient who had just given birth to a stillborn infant with erythroblastosis fetalis must have become sensitized against a red cell factor in her baby which was inherited from its father. This brilliant and logical explanation stimulated further investigations of intragroup transfusion reactions. After 1941, when Landsteiner and Wiener published their studies on a new human blood type (the Rh system), its relation to the formerly mysterious transfusion reactions and especially to the development of erythroblastosis fetalis became evident. The entire field of immunohematology was stimulated to re-exploration and in the next dozen years or so another eight or nine independent families of blood group factors were uncovered. More than a hundred specific subtypes of these have now been described, and this has led to important advances in anthropology, legal medicine, transfusion therapy and homotransplantation.

Specific improvement in the management of erythroblastosis fetalis occurred with the development of new and more sensitive tests for Rh antibodies. The antiglobulin test of Coombs made the diagnosis of sensitization in the Rh-negative woman and erythroblastosis fetalis in her newborn infant entirely reliable. After 1946, it became possible to protect the live-born infant from the dis-

*Ortho Research Laboratories, Raritan, New Jersey.

astrous effects of severe hemolytic anemia through the use of exchange transfusion. This reduced the mortality from anemia and cardiac failure from 30 percent or more to a present level of 5 percent or less. The neonatal complication of jaundice from hyperbilirubinemia which so often resulted in kernicterus and death or, if less severe, in cerebral palsy, mental retardation or some specific nerve damage, with an incidence of over 20 percent, is now completely preventable.

Progress has also been made in the rescue of the one of five infants with severe erythroblastosis fetalis who might die *in utero* from cardiac failure and fetal hydrops. Amniocentesis yields fluid which is easily analyzed for its bilirubinoid pigment content. A high pigment level or a rising value on repeated taps has proven an accurate index of severe hemolytic disease *in utero*. Early delivery, if the thirty-fifth week of gestation has been reached, has saved some infants. For earlier gestational products, the bold approach first tried by Liley of New Zealand, consisting of intrauterine transfusion of the fetus via its peritoneal cavity, seems to be the only treatment available at present. From several medical centers where this is being practiced, the results indicate that 40 to 60 percent of fetuses with severe hemolytic disease can be rescued.

While the development of methods of treating erythroblastosis fetalis has led to satisfying alterations in its severity and outcome, the time required to care for each sensitized woman and to treat the affected infant (often with multiple exchange transfusions) has been formidable. The statistical incidence of sensitized Rh-negative women is between 1 and 1.5 percent. In California, with 350,000 births per year, even at the lower figure there would be 3,500 infants with erythroblastosis fetalis. This represents a significant pediatric case load. For the individual family in which a case has occurred and is likely to recur, it often means a serious financial burden, a dreaded psychological handicap and a limitation in family.

As proved lately in some 36 medical centers in the United States, and in an equally large number in Canada and in Europe, this worrisome disease can now be eliminated by the use of a single intramuscular injection of 1 ml of anti-Rh gamma globulin (RhoGAM®) containing 300 μgm of this antibody. When given to an Rh-negative unsensitized woman within 72 hours after delivery of an Rh-positive baby, this concentrate will block active immunization and thereby prevent erythroblastosis fetalis in the next pregnancy. The details of the experimental trial of anti-Rh gamma globulin concentrate in suitable cases have been reported previously by Freda, Gorman and Pollack of New York City in 1966 and by Clarke and his associates of Liverpool in 1967. Each group started independently to try to protect Rh-negative unsensitized women from immunization by their Rh-positive newborn babies. Their results were amazingly successful. In this country, the specific gamma globulin (RhoGAM®) was prepared under the supervision of Dr. Pollack of the Ortho Research Foundation of Raritan, N.J. This pharmaceutical laboratory supplied not only Freda and Gorman but 35 other groups of investigators all over the United States with their gamma globulin concentrate for trial use. The results to date, as compiled by Dr. William Ascari, Director of Clinical Research at the Ortho Laboratories, show that in almost two thousand cases where RhoGAM® was used, sensitization and anti-Rh production were prevented, whereas in more than a thousand cases in which no protection was used, sensitization developed in the expected number of about 7 to 8 percent.

Elsewhere in this issue of CALIFORNIA MEDICINE, Jennings and coworkers report experience with this concentrate at one of the 43 cooperating centers in the United States and abroad which tried RhoGAM®. Obviously a preventive treatment which promises almost 100 percent success in saving the Rh-negative unsensitized woman from immunization through pregnancy is an exciting development. It also becomes an important public health measure, since about 8 percent of childbearing women are at risk, according to Clarke's figures. Allowing for the number of women of Oriental and African background (predominantly Rh-positive) this figure might be reduced to 6.5 percent in California, yielding an estimate of about 20,000 each year who might need protection after childbirth.

The source of this concentrate is human plasma from sensitized Rh-negative men accidentally or deliberately given Rh-positive blood, or women also sensitized by transfusion or, much more commonly, by pregnancy. To compound the difficulty, the donors of this source plasma must have anti-Rh titers of 1000 or more whereas most titers are less than 50. To supply the need of California would require about 20,000 one-milliliter doses

of the specific gamma globulin per year. This would demand a pool of about 1,300 liters of the high-titered plasma, or 5,200 donations of a pint of blood. Even if each donor were bled five times yearly, more than 1000 high-titered persons would be needed for California. Fortunately, the problem of donor procurement is not so formidable. By the technique of plasmapheresis, donors can be used every week or two and 500 ml of plasma can be harvested each time by withdrawing two pints of blood in sequence at each visit and returning the red cells immediately. By this method, a valuable donor can be the source of as much as 20 liters of plasma a year, so that 65 donors might supply the needed pool. However, restimulation of these anti-Rh serum producers through the use of injections of small amounts of Rh-positive cells would be necessary.

Considering the numerous difficulties already enumerated and several others not mentioned, the years of research and the free distribution of the product for clinical trial in thousands of cases, the present cost of $45 per milliliter for the commercial anti-Rh gamma globulin (RhoGAM®) is not unreasonable. At this rate, California would need to expend almost $1,000,000 for material alone. The necessary testing of each woman and her infant before using this prophylaxis would add to the cost per patient and this still would not include the cost of professional care.

To try to reduce this high cost of protection for Rh-negative women, departments of maternal and child health in several states are considering ways and means of procuring their own anti-Rh gamma globulin concentrate. The Division of Biologic Laboratories of the Department of Public Health of Massachusetts, with the participation and support of the Maternal and Child Health Department of the City of Boston, and in cooperation with the Blood Grouping Laboratory and the Children's Hospital in Boston, has already processed its first lot of serum and expects to be able to take care of its needs at a quarter of the cost of the commercial serum. Other public health departments should eventually be able to do likewise.

Whatever the cost, it is obviously necessary now to protect every woman who is at risk from Rh sensitization. Very likely we can expect that protection against Rh-sensitization will be practiced widely and soon. Numerous articles about it have appeared in state and national medical journals. In addition, a few feature stories about this important medical advance have been published in magazines, daily papers, and Sunday supplements. Rh-negative women are and will be demanding "the Rh serum" after delivery. Thus prompted, no physician can afford to be tardy in offering his patients the latest method of prophylaxis against Rh immunization. When prophylaxis is universally carried out, Rh disease or erythroblastosis fetalis a generation from now will be of historic interest only.

LOUIS K. DIAMOND, M.D.
Department of Pediatrics, University of California-San Francisco Medical Center

A Word of Thanks

MOST PRACTICING PHYSICIANS have probably never heard of the Health Insurance Benefits Advisory Council (HIBAC). Its chronicle is recounted elsewhere in this issue. The government officials charged with the administration of Medicare (Title XVIII of the Social Security Act) have relied heavily upon advice sought and received from qualified persons outside of government. Many Californians are among those who have contributed their professional expertise both officially and unofficially.

We who work in the vineyards of medical practice are much in the debt of those of our members who have taken the time, first to become qualified in the technology of this complex field, and then to spend the countless hours it has taken to put their knowledge and experience to good use. It is we and our patients who have benefited, and we are pleased and proud to take this opportunity to commend those physicians who have undertaken this much needed yet essentially selfless task.